Original Article

Prospective, Open-Label, Randomized, Parallel Group, Comparative Clinical Study of Two Topical Formulations of Diclofenac Diethylamine in the Treatment of Acute Painful Musculoskeletal Conditions

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Abstract

Background: Oral nonsteroidal anti-inflammatory drugs have been used in the management of musculoskeletal pain due to inconsistent skin penetration of topical formulations. The quick penetrating solution of diclofenac is a novel topical solution of diclofenac diethylamine (4.64%), which has increased skin penetration. The present study was designed to compare the efficacy and safety of quick penetrating solution of diclofenac with diclofenac gel in patients with acute musculoskeletal pain. **Materials and Methods:** A randomized controlled clinical trial was conducted in 140 patients suffering from acute musculoskeletal pain who were randomized to receive diclofenac diethylamine 4.64% w/v topical solution (Group A) or diclofenac diethylamine 1.16% gel (Group B). The pain intensity difference (PID) between patients in both groups at rest and during movement of the affected area on day 3 and day 7 after injury was noted using the visual analog scale (VAS) and were compared with the baseline. A comparison of the requirement of oral rescue analgesics and adverse effects in both groups was also carried out. **Results:** The PID in VAS from baseline was significantly better in patients in Group A than patients in Group B on days 3 (3.74 and 2.42; $P < 0.05$) and 7 (6.8 and 5.54, $P < 0.05$), respectively, at rest. The PID in VAS from baseline was significantly better in patients in Group A than patients in Group B on day 3 (4.05 and 2.65; $P < 0.05$) and day 7 (7.34 and 6.00, $P < 0.05$), respectively, during movement. The number of patients requiring rescue medications were significantly lower in Group A ($n = 1$) compared to Group B ($n = 16$) ($P < 0.05$). **Conclusions:** Diclofenac diethylamine 4.64% w/v is more effective in relieving acute pain in painful musculoskeletal conditions in comparison with diclofenac diethylamine topical gel 1.16% w/w with lesser requirement of rescue analgesics and minimal adverse effects.

Keywords: Diclofenac diethylamine, nonsteroidal anti-inflammatory drug, quick penetration solution, topical, visual analog scale

Introduction

Acute musculoskeletal injuries constitute a vast majority of patients visiting an orthopedic clinic. They are known to cause pain, restriction of movements, and significant functional disability. The management of such injuries involves rest, immobilization, compression, elevation of the extremity, and anti-inflammatory medications. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone for musculoskeletal pain management.[1] Available in oral, parenteral, and topical formulations, NSAIDs have revolutionized the management of acute musculoskeletal injuries. Oral NSAIDs are known to cause carry significant dose-dependent adverse effects involving cardiovascular, renal and hematological systems.[2] This has justified the use of topical formulations of NSAIDs in the management of acute musculoskeletal injuries. One of the most commonly used topical NSAID is diclofenac sodium. Topical diclofenac may limit its the dose related adverse effects known to oral

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and injectable forms by reducing the systemic distribution.[3] Topical diclofenac formulations including creams, gels or aerosol sprays have been recommended over oral diclofenac by various guidelines.[4-6] It has been found that the commercially available diclofenac gels have a bioavailabilty of 10% and skin penetration depth of only 3–4 mm.[7] The quick penetrating solution of diclofenac topical solution manufactured using nonaqueous, nonvolatile solvents facilitates easier skin penetration. A large comparative clinical study evaluating the safety and efficacy of diclofenac topical solution in comparison to diclofenac gel applied locally in 230 patients of various acute musculoskeletal injuries showed that the time to onset of pain relief was significantly shorter with diclofenac topical solution as compared to diclofenac gel with significantly more percentage of patients on diclofenac topical solution (80%) reporting reduction in their pain compared to those on diclofenac gel (55.7%).[8] On this premise, it was planned to conduct a randomized control trial (RCT) to compare diclofenac diethylamine 4.64% w/v topical solution and diclofenac diethylamine 1.16% w/v topical gel in patients with acute musculoskeletal injuries to evaluate the efficacy and safety data in actual clinical settings.

Materials and Methods

The current study was planned and executed as a prospective, randomized controlled clinical trial to study the efficacy and safety of diclofenac diethylamine 4.64% w/v topical solution and diclofenac diethylamine 1.16% w/v topical gel in patients with acute musculoskeletal injuries in a tertiary care center of Western India (Clinical Trail Registry of India RCT trial number CTRI/2018/04/013316). The primary objective was to evaluate the pain intensity difference (PID) from baseline (before starting treatment) between patients receiving diclofenac diethylamine 4.64% w/v topical solution and diclofenac diethylamine 1.16% w/v topical gel at rest and during movement of the affected area on day 3 and day 7 after injury using the visual analogue scale (VAS). The secondary objectives were to compare the requirement of oral rescue analgesics and adverse effects in both groups. The investigators examined the patients of acute musculoskeletal injuries in the Orthopedic Outpatient and Casuality Department of a busy tertiary care center in Western India. The patients who satisfied the inclusion and exclusion criteria were invited to participate in the study after obtaining a written informed consent. All skeletally mature patients of both genders between 18 and 70 years of age with acute painful musculoskeletal pain were included in the study. Patients with deep abrasions, lacerations and fractures around the area of affliction and patients with known adverse reaction to topical diclofenac preparations were excluded from the study. The approval of Institutional Ethics Committee was obtained before starting the trial. The patients were randomized to two treatment Groups A and B, receiving diclofenac topical solution 4.64% w/v and diclofenac topical gel 1.16% w/w respectively using computer generated random number tables. The study was conducted in an outpatient basis since patients were admitted in the center of study for orthopedic injuries in cases they required surgical management. The trial was conducted in a single blinding format where the patients were unaware of the formulation they were receiving whereas the investigators who were the clinicians knew the type of intervention the participants were undergoing. Basic demographic details noted were age and gender. A total of 82 patients were enrolled in Group A and 75 in Group B. In both the groups, the respective topical formulations were applied four times a day after washing the area with soap and water and allowed to dry. Other adjuvant modalities in the management of acute musculoskeletal injuries including rest, icing, compression, and elevation of the affected area were advised in both the groups at the time of initial enrollment in the study. Although cast immobilization was not done, rest to the injured part was ensured by arm sling pouches for shoulder and elbow contusions, wrist brace for wrist contusions, open patella knee brace for knee contusions, and ankle brace for ankle contusions. Nonweight-bearing ambulation was allowed using elbow crutches or walking frames in lower limb afflictions. Daily feedback was taken from the patients in both groups telephonically to ensure their adherence in the trial and to ensure the use of adjuvant modalities in the form of rest, icing, and elevation. All patients were examined after 3 days and 7 days in the Outpatient Department. No oral analgesics were given until the patient had a VAS score of 8 on day 3 at rest or movement in both the groups. All such patients were prescribed Ibuprofen 400 mg tablets as the oral analgesic to be taken six hourly. The VAS score was noted in every patient at the baseline and on day 3 and day 7 in a pro forma. On the same days, local and systemic adverse events related (probably or certainly) to the topical diclofenac diethylamine product were recorded in the proforma by the investigators. Occurrence of such adverse events was compared between the two treatment groups. Out of a total of 172 patients considered to be included in the trial, 152 were randomized in to Group A (82 patients) and B (75 patients) and intervened. After 17 patients (12 in Group A and 5 in Group B) were lost to follow up or discontinued adhering to the protocol, data analysis of 140 patients (70 in each group) was carried out. The diagnosis of the patients with the number of cases in both groups were as follows: in Group A, there were 21 cases of knee contusion, 18 cases of ankle sprain, 12 cases of foot contusion, 9 cases of shoulder contusion, 6 cases of elbow contusion, and 4 cases of wrist contusion. In Group B, there were 24 cases of knee contusion, 16 cases of ankle sprain, 14 cases of foot contusion, 8 cases of shoulder contusion, 5 cases of elbow contusion, and 3 cases of wrist contusion. The procedure is as depicted in the CONSORT diagram as Figure 1. The data collected were statistically analyzed using the Statistica 11 software (Dell Software, Round Rock, Texas, USA), and the results were tabulated.

Results

The patients in both Groups A and B were similarly distributed in the demographic parameters of age and sex ($P > 0.05$; unpaired *t*-test and Chi-square test). The baseline VAS scores

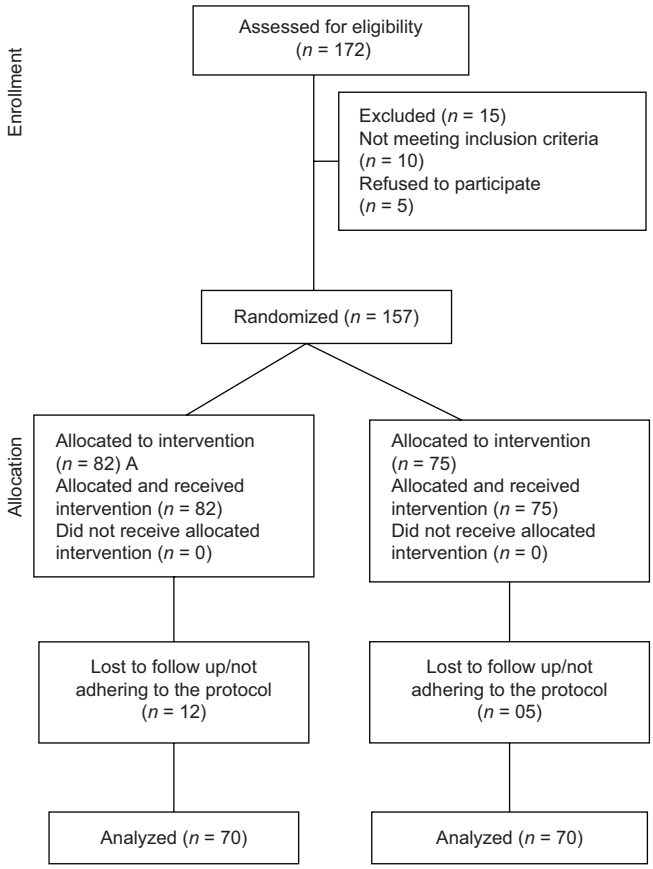

Figure 1: CONSORT diagram

Table 1: Demographic comparison

Parameter	Group A (*n*=70) Topical Diclofenac Solution	Group B (*n*=70) Diclofenac Topical Gel	*P*
Age in Years	36.68±12.62	34.65±11.84	0.3285*
Gender (Males/Female)	39/31	42/28	0.60762†
Baseline VAS on Rest	8.34±1.44	8.45±1.41	0.636*
Baseline VAS on movement	9.28±1.07	9.6±0.874	0.0604*

* - unpaired 't' test , †- Chi-square test

of patients (at rest and on movement) in both groups were comparable ($P > 0.05$; unpaired *t*-test). The same is represented in Table 1. The number of patients in both groups according to the anatomical location of the injury were also comparable as represented in Table 2 ($P > 0.05$; Chi-square test). on evaluating the primary objective of comparison of the efficacy of topical diclofenac solution 4.64% w/v and diclofenac topical gel 1.16% w/w in reducing the intensity of pain at rest on day 3 and 7, it was found that the patients who were treated with topical diclofenac solution 4.64% w/v (Group A) experienced significant improvement from their baseline pain intensity at rest as compared to diclofenac topical gel 1.16% w/w (Group B) on day 3 (3.74 and 2.42; $P < 0.05$) and day 7 (6.8 and 5.54, $P < 0.05$) as determined by the PID in VAS using the *t*-test. The results are depicted in Table 3. Similarly, on comparison of the efficacy of topical diclofenac solution 4.64% w/v and diclofenac topical gel 1.16% w/w in reducing the intensity of pain on movement of the affected area on day 3 and 7, it was found that the patients who were treated with topical diclofenac solution 4.64% w/v (Group A) experienced significant improvement from their baseline pain intensity on movements compared to diclofenac topical gel 1.16% w/w (Group B) on day 3 (4.05 and 2.65; $P < 0.05$) and day 7 (7.34 and 6.00, $P < 0.05$) as determined by the PID in VAS using the *t*-test. The results are as depicted in Table 4. On evaluating the secondary objective of requirement of rescue analgesia in both groups, the number of patients requiring rescue medication in Group A was significantly lower (1) than the proportion of patients requiring rescue medication in Group B (16) during the overall duration of study ($P < 0.05$; Chi-square test) The result is depicted in Table 5. The incidence of treatment emergent adverse events did not differ significantly in both the groups. No systemic adverse events were reported; all the adverse reaction reported were local application site reaction. The major adverse events reported were redness and itching followed by burning sensation. In total, 11 patients reported the local adverse reaction to the treatment, incidence being lower in topical diclofenac 4% solution as compared to topical diclofenac 1.16% gel (four patients vs. seven patients respectively), the results of which were comparable by Chi-square test ($P > 0.05$) as depicted in Table 6.

Discussion

NSAIDs are the most commonly used medications used in the management of acute musculoskeletal injuries. Topical NSAIDs are a form of targeted delivery method developed essentially to reduce the systemic absorption and associated toxicity without losing its local effect and benefit. Commonly available topical NSAIDs include diclofenac preparations, ketoprofen gel, piroxicam patch/cream, and ibuprofen cream/gel among others.[9] Diclofenac has however been the most widely used and studied topical NSAIDs.[10] The mechanism of action of topical diclofenac is by inhibition of the cycloxegenase isoenzymes and thereby decreasing the synthesis of pro-inflammatory prostaglandins, and at higher concentrations, it is postulated that it acts as a sodium channel blocker inhibiting the nociceptive afferent fibers and result in analgesia.[11] The commonly available topical diclofenac preparations include diclofenac sodium 1% gel, diclofenac diethylamine gel 1.16%, MIKA diclofenac spray 4% gel, diclofenac dimethyl sulfoxide (DMSO) lotion, and diclofenac epolamine (diclofenac hydroxyethylpyrrolidine) patch. It has been found that the commercially available diclofenac gels have a bioavailabilty of 10% and skin penetration depth of only 3–4 mm.[7] Lack of effectiveness of currently available topical formulations of NSAIDs compels the use of oral NSAIDs for the management of musculoskeletal pain, despite of their side effects.[11] Most available diclofenac topical gels are aqueous

Table 2: Comparison of diagnosis in both groups

Parameter	Group A (*n*=70)	Group B (*n*=70)	*P*
Contusion Knee	21	24	
Ankle Sprain	18	16	0.98†
Contusion Foot	12	14	
Shoulder Contusion	09	08	
Elbow Contusion	06	05	
Wrist Contusion	04	03	

†- Chi-square test

Table 3: Comparison between groups for change in pain intensity (baseline-day 3 and baseline-day 7) at rest as determined by visual analog scale

Visits	Mean (Group A)	Mean (Group B)	*t*	*P*
At day 3	−3.742857	−2.428571	−9.021342	0
At day 7	−6.8	−5.542857	−4.849568	0.000003*

**t*-test

Table 4: Comparison between groups for change in pain intensity (baseline-day 3 and baseline-day 7) on movement as determined by visual analog scale

Visits	Mean (Group A)	Mean (Group B)	*t*	*P*
At day 3	−4.057143	−2.657143	−6.110488	0
At day 7	−7.342857	−6	−4.990123	0.000002*

**t*-test

Table 5: Comparison between groups for rescue medications intake

Use of rescue analgesic medication	No	Yes	Proportion of patients	*P*
Group A (*n*=70)	69	1	1.42	0.00010*
Group B (*n*=70)	54	16	22.85	

*Chi-square test

Table 6: Summary of treatment emergent adverse events

Description of adverse event	Incidence in Group A	Incidence in Group B	*P*
Redness	2	4	0.62886*
Itching	2	2	
Burning	0	1	

*Chi-square test

in nature and their skin is not sufficient to reduce the pain effectively.[11] Diclofenac topical solution is a quick penetrating solution of diclofenac manufactured using nonaqueous, nonvolatile solvents which facilitates skin penetration. Its higher concentration of diclofenac and presence of nonaqueous solvents have been proven to promote higher tissue penetration of diclofenac.[12-14] A multicenter RCT conducted across 5 hospitals in 230 patients with acute musculoskeletal injuries evaluating the safety and efficacy of diclofenac topical solution in comparison to diclofenac gel showed that the time to onset of pain relief was significantly shorter with diclofenac topical solution as compared to diclofenac gel with significantly more percentage of patients on diclofenac topical solution (80%) reporting reduction in their pain compared to those on diclofenac gel (55.7%).[8] On this premise, it was planned to conduct a prospective, randomized, clinical trial to study the efficacy and safety of diclofenac diethylamine 4.64% w/v topical solution and diclofenac diethylamine 1.16% w/v topical gel in patients with acute musculoskeletal injuries. The demographic features and the preintervention VAS scores of patients in both groups were comparable which shows that the groups were randomized optimally. The mean age of patients in Group A and Group B were 36.68 ± 12.62 and 34.65 ± 11.84, respectively. There were 39 males and 31 females in Group A and 42 males and 28 females in Group B. The baseline VAS scores at rest in Group A and B were 8.34 ± 1.44 and 8.45 ± 1.41, respectively, and VAS scores on movement were 9.28 ± 1.07 and 9.6 ± 0.874, respectively. The demographic features and the preintervention VAS scores of patients in both groups were comparable ($P > 0.05$; unpaired *t*-test) which shows that the groups were randomized. The number of patients suffering from various conditions were comparable on both groups as depicted in Table 2, showing an optimal distribution in both the groups. The mean PID on rest assessed using VAS in Group A was 3.74 and 6.8 on days 3 and 7 compared with the baseline VAS score of 8.34 ± 1.44. Meanwhile, the mean PID on rest in Group B on rest was 2.42 and 5.54 on days 3 and 7 compared with the baseline VAS score of 8.45 ± 1.41. The mean PID on movement of the affected area analyzed using the VAS in Group A was 4.05 on days 3 and 7.34 on day 7 compared with the baseline VAS of 9.28 ± 1.07. Similarly, the mean PID on movement in Group B also showed a drop of by 2.65 on days 3 and 6 on day and compared with the baseline value of 9.6 ± 0.87. Hence, both the topical formulations of diclofenac were found to be effective in the management in acute painful musculoskeletal conditions when compared with baseline. However, topical solution of diclofenac 4.64% w/v was significantly better than diclofenac topical gel 1.16% w/w in the primary outcome of reducing the intensity of pain at rest and movement as depicted in the results. The statistical analysis revealed that the patients who were treated with topical diclofenac solution 4.64% w/v experienced significantly more improvement in their baseline pain intensity both while movement and at rest as compared to diclofenac topical gel 1.16% w/w on day 3 ($P < .05$) and day 7 ($P < .05$) as determined by VAS. Oral NSAIDs in the form of tablet Iboprufen (400 mg) for patients who had severe pain (VAS >8 in the affected area at rest on day 3 of intervention in both groups) was prescribed as rescue analgesia. It was observed that more number of patients in Group B required rescue analgesics as compared to patients in Group A. The difference was statistically significant ($P < 0.05$) favoring topical diclofenac sodium (4.64% w/v). All the local adverse reactions reported were self-limiting/reversible in nature, redness at the application site being the major adverse reaction followed by itching and burning sensation. The incidence of

treatment emergent adverse events did not differ significantly in both the arms of treatment ($P > 0.05$; Chi-square test).

Conclusions

This prospective, randomized controlled trial was conducted to compare the efficacy and safety of diclofenac diethylamine 4.64% w/v topical solution and diclofenac diethylamine 1.16% w/v topical gel in 140 patients with acute musculoskeletal injuries. It can be concluded from the results and observations that topical solution of diclofenac diethylamine 4.64% w/v is more effective in relieving the acute pain in painful musculoskeletal conditions in comparison with diclofenac diethylamine topical gel 1.16% w/w with lesser requirement of rescue analgesics and minimal local and no systemic side effects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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